Atypical Glandular Cells of Undetermined Significance (AGUS)

Interobserver Reproducibility in Cervical Smears and Corresponding Thin-Layer Preparations

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Abstract

Five panelists independently reviewed 135 consecutive conventional cervical smears (CPs) originally classified as atypical glandular cells of undetermined significance (AGUS). A thin-layer slide (TP), prepared from the residual material, also was reviewed in each case. All patients underwent colposcopy that yielded at least 1 histologic specimen.

Three or more of 5 reviewers retained the AGUS interpretation for 29% of CPs and 12% of the corresponding TPs. Interobserver variability in frequency of use of AGUS was marked, and interobserver agreement was poor. Agreement was improved for cases cytologically interpreted as a high-grade lesion, especially in TPs. Four of 5 reviewers retained the AGUS classification in CPs for all 7 biopsy-proven neoplastic glandular lesions. Of 95 CP interpretations made by 5 reviewers in the 19 histologically diagnosed high-grade lesions, 8 were "negative/reactive" and 6 were AGUS "favor reactive."

AGUS is a poorly reproducible cytologic interpretation. Although most neoplastic glandular lesions may be distinguished by cytopathologists experienced in this area from mimics originally considered AGUS, attempts to increase the diagnostic specificity of AGUS may diminish sensitivity for an underlying high-grade precursor. Interobserver agreement was better for TPs than for the corresponding CPs. However, the split-sample TP slides may not have been fully comparable to the CPs.

The incidence of uterine cervical adenocarcinoma is increasing in the United States.[1,2] Cervical cytologic screening offers the potential for its prevention by detecting the precursor, adenocarcinoma in situ (AIS).[3,4] In the Bethesda system,[5] glandular atypia that exceeds that of reactive changes but is not diagnostic of invasive adenocarcinoma has been designated "atypical glandular cells of undetermined significance" (AGUS). This designation may be further qualified to indicate whether an endocervical or endometrial abnormality is suspected and, in the former case, whether a reactive or a neoplastic process is favored. Although the cytologic criteria for AIS have been amply described,[6-10] AGUS is a problematic diagnosis. Because of the pitfalls inherent in the cytologic interpretation of atypical glandular cells,[8-20] most patients for whom AGUS is interpreted in a smear have only an inconsequential reactive endocervical process, yet a significant minority harbor a high-grade precursor lesion, which is usually squamous cervical intraepithelial neoplasia (CIN), rather than glandular.[21-37] In addition, although the reproducibility of an AGUS interpretation has not been studied thoroughly, one report[30] found that AGUS, like its squamous counterpart atypical squamous cells of undetermined significance (ASCUS), was poorly reproducible.[38,39]

In a previous study, morphologic findings in 137 smears initially reported as AGUS in routine community screening at 12 centers in the Kaiser Permanente Medical Care Program (Oakland, CA) were examined in detail and compared with histopathologic findings.[33] The main conclusions from that study were as follows: (1) High-grade cervical precursor lesions are detected about twice as frequently in women with AGUS compared with those with ASCUS in a general community screening setting. (2) Most high-grade lesions

associated with AGUS are CIN 2/3. (3) Use of strict cytologic criteria for AGUS may enhance the specificity of this designation for detecting AIS. The last conclusion was reached tentatively, allowing for the possibility that AGUS interpretations by other cytopathologists cognizant of these criteria may not be reproducible. Therefore, the present study was initiated to test the reproducibility of AGUS using these same smears. Reviewers' smear interpretations were compared with histologic outcomes from the previous study. The reproducibility of concurrently obtained thin-layer preparations also was assessed.

Materials and Methods

Details of the study design, approved by the institutional review board of the Kaiser Foundation Research Institute, Oakland, CA, are presented elsewhere.[33] In brief, 137 of 225 consecutive patients with a conventional Papanicolaou smear (CP) report of AGUS, identified in a cohort of 46,009 women, are included in this analysis. CPs and ThinPreps (TPs; Cytyc, Boxborough, MA), prepared only in cases with AGUS on CP from the residual material on the CP sampling device after smears were prepared, were coded, packaged into 4 sets, and distributed by mail to 5 reviewers at 4 institutions. Because of logistic problems, only 135 CP and 134 TP slides of the original 137 pairs were circulated. Furthermore, only 133 CPs and 131 TPs were seen by all 5 reviewers, the remainder having been seen by 4 of the 5. All reviewers (T.M.D., N.E.J., J.F.K., K.R.L., M.E.S.) have an interest in the cytologic interpretation of glandular lesions and were aware of the initial interpretation of AGUS on CPs but not the corresponding histologic diagnoses. At the time of the reviews, the CP and TP slides were not matched with one another except that 1 reviewer (M.E.S.), as a part of his participation in the original study, was aware of the matching CPs and TPs.

Reviewers used their own criteria for classification and did not communicate with one another before or during the study. Interpretations were recorded using a modified Bethesda classification system that included subcategories within AGUS and ASCUS. Within the AGUS category, reviewers were asked to specify whether they thought the abnormal cells to be endometrial or endocervical and, for those considered endocervical, whether the cells were most likely to be "reactive," "neoplastic," diagnostic of AIS, or could not be further specified. Case-report forms with the reviewers' diagnoses were assembled at the Kaiser Permanente Northern California Region Division of Research (Oakland, CA), where CP and TP cases were matched with each other and CP interpretations were matched with the histologic interpretations from the previous study. Because the method used to prepare TPs used only residual material from the sampling device after smears were prepared, potential lesions may have been underrepresented in some of them compared with CPs. Therefore, TP interpretations were not compared with biopsy outcomes.

Table 1
Agreement Among Five Reviewers on the Interpretation of AGUS in Smears and Corresponding Thin-Layer Preparations in Cases Originally Classified as AGUS in Conventional Smears

No. of Reviewers Diagnosing AGUS in an Individual Case	Percentage of 133 Conventional Smears	Percentage of 131 Corresponding Thin-Layer Preparations
None	20.3	48.1
1	21.8	28.2
2	30.1	12.2
3	15.0	7.6
4	9.8	2.3
All 5	3.8	2.3

AGUS, atypical glandular cells of undetermined significance.

The reviewers' cytologic interpretations were tabulated for CPs and the corresponding TPs. Kappa statistics for pairwise interrater agreement (unweighted) were calculated separately for CPs and TPs in 2 separate analyses. In the first analysis, data were dichotomized into AGUS (including 7 diagnoses of adenocarcinoma) as opposed to all other interpretations. In the second analysis, results were dichotomized into high-grade lesions on cytology (ASCUS "favor high-grade squamous intraepithelial lesion [HSIL]," HSIL, AGUS "favor neoplasia" or AGUS "not specified," AIS, or carcinoma) as opposed to all other interpretations. Kappa values less than 0.4 were considered to reflect poor agreement; those between 0.4 and 0.7, good agreement; and those more than 0.7, excellent agreement. Finally, the combined CP interpretations for all 5 reviewers and for each of the 5 reviewers' individual CP interpretations of AGUS were compared with the histologic findings. All analyses were done using Stata Statistical Software, release 6.0 (Stata, College Station, TX).

Results

Reviewers' Cytologic Interpretations

In cases seen by all 5 reviewers, the AGUS classification was not retained by any reviewer in 20.3% of CPs and 48.1% of TPs and was retained by all 5 reviewers in 3.8% of CPs and 2.3% of TPs. At least 3 of 5 reviewers agreed with the original diagnosis of AGUS in 28.6% of CPs and in 12.2% of TPs **Table 1**. The range of individual reviewer agreement with the original interpretation of AGUS was

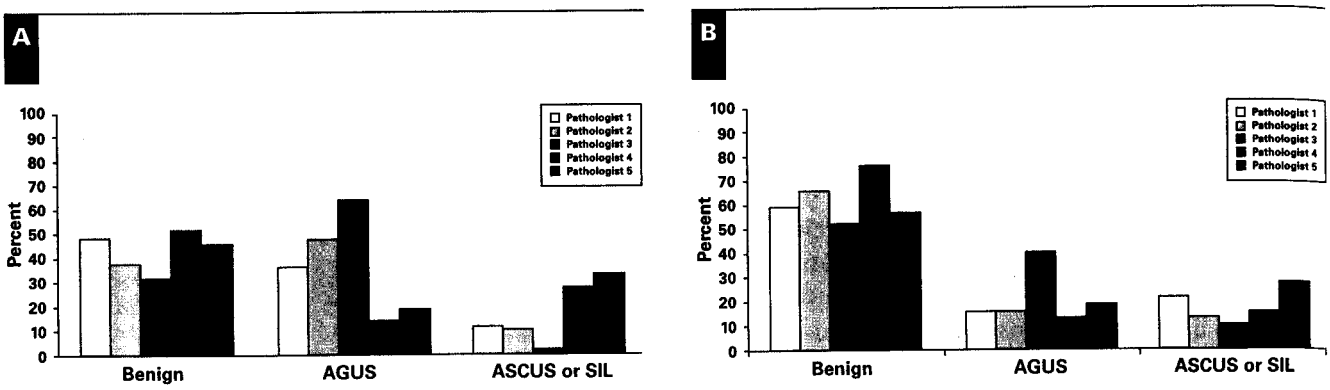

Figure 1 **A**, Percentage of reviewed conventional smear interpretations, by pathologist, in cases originally classified as atypical glandular cells of undetermined significance (AGUS). **B**, Percentage of corresponding thin-layer preparation interpretations, by pathologist, in cases originally classified as AGUS by conventional smears. ASCUS, atypical squamous cells of undetermined significance; SIL, squamous intraepithelial lesion.

from 14.7% to 65.4% of CP samples (median, 36.7%) and from 10.3% to 36.6% of TP samples (median, 16.3%). Individual reviewers reclassified from 31.6% to 55.1% of CP cases and from 54.3% to 74.2% of TP cases as either normal/reactive or benign endometrial cells; they reclassified from 2.9% to 33.6% of CPs and 9.7% to 27.4% of TPs as squamous lesions (HSIL, low-grade squamous intraepithelial lesion, or ASCUS) **Figure 1**.

Interobserver Agreement

Interobserver agreement for AGUS, including all subcategories, was poor for all pairwise combinations for both CPs and TPs, except that reviewers 1 and 2 had good agreement using TP **Table 2**. Interobserver agreement for the diagnosis of a high-grade lesion was good in 4 of 10 pairwise combinations in CPs and poor in the other 6; agreement was good in 9 of 10 combinations in TPs and poor in 1 (Table 2).

Cytologic Interpretations Compared With Histologic Findings

The cumulative CP cytologic interpretations of all 5 reviewers, tabulated by histologic category, are given in **Table 3**. In the 12 histologically diagnosed cases of CIN 2/3, 41% of reviewers' smear interpretations were AGUS and 43% were HSIL. In the 6 cases of AIS (including 1 "glandular atypia"), 10% were interpreted as HSIL and 89% as AGUS. When all 19 histologically proven high-grade glandular or squamous lesions and all 5 reviewers' CP interpretations were considered (95 possible interpretations), there were 8 (8%) false-negative interpretations and

Table 2
Pairwise kappa Statistics

	Smears				Thin-Layer Preparations			
	Observer				Observer			
Observer	2	3	4	5	2	3	4	5
AGUS interpretations								
1	0.20	0.27	0.24	0.12	0.47	0.29	0.36	0.28
2		0.28	0.22	0.14		0.15	0.36	0.25
3			0.14	0.08			0.07	0.13
4				0.23				0.16
Cytologic interpretations of a high-grade lesion*								
1	0.34	0.27	0.51	0.45	0.53	0.57	0.52	0.56
2		0.29	0.38	0.34		0.34	0.55	0.44
3			0.44	0.21			0.46	0.58
4				0.41				0.54

AGUS, atypical glandular cells of undetermined significance.
* Includes AGUS favor neoplasia or not specified, adenocarcinoma in situ, high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells of undetermined significance favor HSIL, and carcinoma.

Table 3
Combined Cytologic Interpretations of Conventional Smears by All Five Reviewers in Each Histologic Category: 135 Smears,* 678 Interpretations (Column Percents)†

	Histologic Category				
Combined Interpretations	**WNL (107 Cases)‡**	**CIN 1 (9 Cases)**	**CIN 2/3 (12 Cases)**	**AIS (6 Cases)§**	**Endometrial Carcinoma (1 Case)**
UNS/WNL/BCC (n = 299)	52	38	12	0	20
ASCUS (n = 71)	10	18	5	3	0
LSIL (n = 6)	0.2	2	5	3	0
HSIL‖ (n = 50)	7	22	43	10	0
AGUS					
Total (n = 252)	37	22	41	89	80
Reactive	18	9	8	3	0
Not otherwise specified	12	9	13	13	20
Neoplastic/AIS¶	5	4	17	70	0
Endometrial	2	0.4	3	3	60

AGUS, atypical glandular cells of undetermined significance; AIS, adenocarcinoma in situ; BCC, benign cellular changes; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; UNS, unsatisfactory; WNL, within normal limits.
* Two smears were reviewed by only 4 of 5 reviewers; in both cases, biopsy diagnoses were WNL.
† Data are given as percentages. Columns may total more than 100% since reviewers sometimes diagnosed both squamous and glandular lesions.
‡ Includes 3 cases diagnosed as "squamous atypia" on biopsy.
§ Includes 1 case histologically interpreted as "glandular atypia" and 2 cases with concomitant CIN 2/3.
‖ Includes 27 diagnoses of ASCUS "favor HSIL."
¶ Includes 7 diagnoses of invasive cervical adenocarcinoma.

Table 4
Individual Reviewer's Interpretations of AGUS* in Conventional Smears as a Percentage of Cases in Each Histologic Category (135 Smears†)

		Histologic Category				
Reviewer	**Total AGUS Interpretations**	**WNL‡ (107 Cases)**	**CIN 1 (9 Cases)**	**CIN 2/3 (12 Cases)**	**(AIS§ (6 Cases)**	**Endometrial Carcinoma (1 Case)**
1	50	33	33	42	100	100
2	66	46	22	67	100	100
3	89	64	56	75	100	100
4	20	11	0	8	100	100
5	27	20	0	67	67	0

AGUS, atypical glandular cells of undetermined significance; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; WNL, within normal limits.
* Includes 7 diagnoses of invasive endocervical adenocarcinoma.
† Two smears were reviewed by only 4 of 5 reviewers; both cases had biopsy diagnoses of WNL.
‡ Includes 3 cases diagnosed as "squamous atypia."
§ Includes 2 cases with concomitant CIN 2/3 and 1 histologically interpreted as "glandular atypia."

6 interpretations of AGUS "favor reactive" (6%). The frequency of each reviewer's CP interpretation of AGUS in each histologic category is given in **Table 4**. All 7 significant glandular lesions (5 AIS, 1 "glandular atypia," and 1 endometrial carcinoma) were retained in the AGUS category by 4 of 5 reviewers.

Discussion

Most CPs that had been classified originally as AGUS were reclassified by a 5-member expert panel as benign. These reclassified diagnoses reflect the findings in the previous study on which this one was based and in most previous studies[21,32-37,40] that a minority of patients with a smear interpreted as AGUS have an underlying neoplastic glandular lesion. However, the wide range in the number and types of reclassified cases among the reviewers led to poor reproducibility of AGUS (Tables 1 and 2, Figure 1). Raab et al[30] previously reported poor reproducibility among 4 expert reviewers using 100 smears originally classified as AGUS. All 4 reviewers in that study agreed with the original AGUS classification in only 15% of cases, whereas none agreed with the original AGUS in 12%. There also was poor reproducibility among reviewers in that study for the prediction of a clinically significant lesion (defined as CIN 1 or greater) in cases originally classified as AGUS. We found mostly poor agreement for the prediction of a high-grade lesion using the original smears. However, agreement was improved and generally good for this prediction using TPs (Table 2).

The authors of the previous study using the same CPs that we examined demonstrated the possibility of reclassifying smears originally interpreted as AGUS more specifically without losing sensitivity for high-grade lesions by using strict cytologic criteria.[33] The 5 reviewers in the present study (including one [M.E.S.] from the previous study) used their own criteria, and although their retention of the original AGUS designation varied widely, they also were able to substantially reduce the total number of cases interpreted as AGUS while retaining most neoplastic glandular lesions in this category, suggesting, as the authors of the previous study found, that expert review may increase AGUS specificity. However, the 8 falsely benign smear interpretations and the 6 interpretations of AGUS "favor reactive" in cases of high-grade CIN or AIS by the "experts" in the present study raise the caution that, although attempts to apply refined criteria for AGUS may increase specificity, this may result in a loss of sensitivity for some high-grade lesions.

The Papanicolaou smear has been reported to be less effective in preventing adenocarcinoma than in preventing squamous carcinoma.[1,2,41,42] The problem of false-negative interpretations of smears from women with high-grade CIN, AIS, or invasive adenocarcinoma has been emphasized.[43-48] Although the present study was not designed to test smear sensitivity, the false-negative interpretations in this study highlight the possibility that underinterpretation of smears, especially those with cells perceived by some to be glandular in origin, may be a significant component of this problem. This possibility is supported by the previous AGUS reproducibility study[30] in which some expert reviewers of AGUS smears significantly underestimated high-grade glandular lesions (only 29% sensitivity by 1 reviewer) and high-grade lesions in general (range of sensitivities, 58% to 95%).

Previous studies of TPs in the diagnosis of uterine glandular lesions, primarily of the cervix, have been fairly small and somewhat contradictory. Ashfaq et al,[49] using direct-to-vial TP samples and 39 historic AGUS CP control specimens, reported an increase in both sensitivity and specificity in 25 AGUS cases in TPs. Bai et al[50] in a similar study reported equal sensitivity but improved specificity for a glandular lesion in 35 TPs interpreted as AGUS. Roberts et al,[51] using split-sample comparisons in 30 cases of AIS, showed a lower sensitivity for TPs. However, 7 of the false-negative TPs reported in that study were diagnosed as "endocervical atypia," indicating, as the authors themselves state, that the diagnostic criteria for AIS in TPs need refinement and may enhance performance once learned. This point also was made by Wilbur et al[52] in a review of comparative cytomorphologic features of CPs and TPs.

The performance of TPs in the present study cannot be assessed fully for several reasons: (1) The study set was limited to TPs prepared only from women with an interpretation of AGUS initially made on a CP. (2) One of the reviewers (M.E.S.) had serially examined the CP and its matching TP, perhaps biasing the TP interpretation. (3) TP slides were prepared from the residual material after the CP had been made, possibly diminishing the relative number of glandular cells in TPs, leading to decreased sensitivity and, paradoxically, possibly improved specificity of AGUS in this set containing relatively few cases of AIS or CIN 2/3. With these disclaimers in mind, we did observe improved interobserver agreement that the lesion was high-grade, either glandular or squamous, with TPs. Also, retention of the original AGUS diagnosis was much less frequent for TPs, with 61% interpreted as benign, suggesting at least the possibility of increased diagnostic specificity using TPs. However, further studies using a direct-to-vial technique for TP preparation and data from clinical practice will be required to verify this possibility.

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